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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,581	12/03/2003	Anthony D. Keefe	23239-544 (ARC-44)	3229

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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
ATTN: PATENT INTAKE CUSTOMER NO. 30623
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
STAPLES, MARK	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
03/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,581	KEEFE ET AL.	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-21 and 77-132* is/are pending in the application.

4a) Of the above claim(s) *97-100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-21, 77-96, and 101-132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/03/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Change of Examiner

1. The examiner of record has changed. Please direct future correspondence to Examiner Staples whose telephone number is (571) 272-9053.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

Claims Pending

3. Applicant's amendment of claims 1, 5-9, 11-18, 77-80, 82-84, 86, 88, 89, 91-93, and 95; and the submission of new claims 101-132 in the paper filed on 10/31/2007 are acknowledged.

Claims 1, 5-21, 77-96, and 101-132 are pending and at issue.

Applicant's arguments filed on 10/31/2007 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 102(b) and 103(a)

4. The rejections of claims 1, 5-21, and 77-96 under 35 USC § 102(b) and § 103(a) are withdrawn. Applicant's arguments with respect to claims have been considered but are moot in view of the new ground(s) of rejection.

Although new rejections are given, it is noted Applicant argues that there is no objective reason to combine the references cited in past Office Actions. However, the objective reasons are listed in the new rejections below.

New Rejections

Double Patenting

5. Applicant is advised that should claim 1 be found allowable, claim 101 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing

one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

New Claim Rejections - 35 USC § 112

6. Claim 111 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 111 recites wherein the substituted guanosine or guanosine is GMP. It is unclear how the unsubstituted GMP can be a substituted guanosine as the two are mutually exclusive.

New Claim Rejections - 35 USC § 103

4. Claims 1, 5-17, 19-21, 77-96, and 101-120, 122-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Pieken et al. (U.S. Patent 5,660,985 previously cited), Brieba et al. (Biochemistry (2000) 39:919-923 previously cited), and Sousa et al (U.S. Patent 6,107,037 previously cited).

Pieken teaches methods of claims 1, 101, and 102 for identifying nucleic acid ligands that bind to a target molecule (see abstract) wherein the nucleic acid ligands comprise a 2'-OMe modified nucleotide (see claim 1 and claim 10, where 2' methoxy groups are expressly claimed),

(a) preparing a transcription mixture comprising a polymerase, modified dNTPs,

wherein at least one NTP is 2' OMe NTP where N can be A, G, C, T or U (by teaching modified pyrimidine and purine bases can be 5-X and/or 2'-Y, here being 2'-Y only with Y being the methoxy group, see column 8 lines 38-63 and Figure 1), magnesium and oligonucleotide transcription templates (see column 16, example 3, lines 10-1 3, where GTP, which is a 2'-OH guanosine triphosphate is used and see claim 10, which requires the use of a 2' OMe NTP),

(b) preparing a candidate mixture of single-stranded nucleic acids by transcribing the one or more oligonucleotide transcription templates under conditions whereby the polymerase incorporates at least one of the one or more 2' O-methyl modified NTPs into nucleic acid molecules of said candidate mixture (see column 16, lines 13-35, where the T7 RNA polymerase is used to incorporate the NTPs and see claim 10, where the modified nucleotides are 2' O-methyl modified NTPs),

(c) contacting the candidate mixture with said target molecule (see column 16, example 3, lines 13-35 and claim 1),

(d) partitioning the nucleic acids having an increased affinity to the target molecule relative to the candidate mixture from the remainder of the candidate mixture (see column 16, example 3, lines 13-35 and claim 1),

(e) amplifying the increased affinity nucleic acids, in vitro, to yield a ligand enriched mixture of nucleic acids, whereby nucleic acid ligands of the target molecule are identified (see column 16, example 3, lines 13-35 and claim 1).

With regard to claims 17, 110, 111, and 130-132, Pieken teaches the use of 2' OH-guanosine which is a substituted guanosine (see column 16, example 3, lines 10-13, where GTP, which is a 2'-OH guanosine triphosphate is used).

With regard to claims 19-20, 85, 94, 112-113, and 127, Pieken teaches the use of PEG (see column 15, line 49).

With regard to claims 21, 87, 96, and 129, Pieken teaches repeating the claim steps (see claim 1).

With regard to claims 77, 83, 92, 125, and 115-119, Pieken teaches a variety of ratios of modified to unmodified nucleotides (see column 13, lines 5-7).

With regard to claims 78, 84, 93, and 126, Pieken teaches the transcription mixture can further comprise spermidine (see Example 2).

With regard to claims 81, 82, 90, 91, 107-109, 122-124, Pieken teaches a purine leader sequence which is 6 nucleotides in length (see SEQ ID NO: 3).

Regarding claims 1, 101, 102, 115-119, and 128, Pieken does not specifically teach the use of modified polymerase and does not teach the use of Y639F or H784A T7 RNA polymerase. Pieken does not specifically teach the use of manganese.

Regarding claims 1, 6-8, and 101-106, 115-119, and 128, Brieba teaches that T7 polymerase mutants at position 784 preferentially utilize2'-OH groups (see abstract) and position 639 mutants rapidly incorporate 2' modified nucleotides (see page 920). Brieba does not specifically teach the use of manganese.

Regarding claims 1, 6-8, 13, 86, 95, 101-106, 115-119, and 128, Sousa teaches the use of manganese and magnesium (see column 15, lines 44-48).

Regarding claims 79, 88, and 114, Sousa teaches: "Preferably, the reactions also contain inorganic pyrophosphatase, which is known to increase the yields in *in vitr*o transcription reactions" (see column 12 lines 41-43).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the T7 RNA polymerase mutants of Brieba in the method of Pieken since Brieba notes that the polymerase with the double mutant is more likely to incorporate 2' substituents (see abstract) and since Pieken would be motivated by this teaching to utilize polymerases with superior properties for incorporation of the desired 2' modified nucleotides.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the magnesium/manganese buffers of Sousa in the method of Pieken and Brieba since Sousa teaches regarding the use of manganese that "In Mn buffer both the w.t. enzyme and Y639F show a reduction in their sensitivity to substitution of dNTPs for rNTPs, consistent with an expectation of reduced substrate discrimination in Mn buffer (see column 22, lines 34-37)." and to use: ". . . inorganic pyrophosphatase . . . to increase the yields in in vitro transcription reactions" (see column 12 lines 41-43). An ordinary practitioner would have been motivated to use manganese buffer in optimized concentrations in order to permit incorporation of the

modified nucleotides expressly desired by Pieken and Brieba. Further, an ordinary practitioner would have recognized that the results optimizable variable of Mn concentration could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific manganese, magnesium, and NTP concentrations was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

7. Claims 18, 89, and 121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pieken et al. (U.S. Patent 5,660,985), Brieba et al. (2000), and Sousa et al (U.S. Patent 6,107,037) in view of Milligan et al. (Methods Enzymol. (1989) previously cited).

Pieken, Brieba, and Sousa teach as noted above.

Pieken, Brieba, and Sousa do not teach the use of GMP in T7 RNA polymerase reactions.

Milligan teaches that when "modified GTP is to be used, it is a good idea to add GMP as a primer if low concentrations of GTP are to be used (see page 59)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use GMP as taught by Milligan when performing the SELEX method of Pieken, Brieba, and Sousa using modified GTP such as 2'-0 methyl GTP since Milligan states that when "modified GTP is to be used, it is a good idea to add GMP as a primer if low concentrations of GTP are to be used (see page 59)." An ordinary practitioner would have been motivated to add GMP whenever low GTP amounts or modified GTP is being used in transcription reactions, in order to ensure the ability of the T7 RNA polymerase enzyme to prime the extension reaction.

Conclusion

8. No claim is free of the prior art.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 7:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
/M. S./
Examiner, Art Unit 1637
March 19, 2008

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637